

CLAIMS

We claim:

[1] A crystal of a whole antibody.

[2] A crystal of a single-chain Fv
5 fragment of an antibody.

[3] A crystal of an Fab fragment of an
antibody.

[4] The crystal according to any one of
claims 1, 2 or 3, wherein said whole antibody or
10 single-chain Fv fragment or Fab fragment is
characterized by β -sheet structural content of the
antibody or fragment, as indicated by a correlation
spectra as compared to the soluble counterpart of said
antibody or antibody fragment, determined by FTIR, that
15 is between about 0.8 and about 1.0.

[5] The crystal according to any one of
claims 1, 2 or 3, wherein said whole antibody or
single-chain Fv fragment or Fab fragment is a
therapeutic antibody or antibody fragment.

20 [6] The crystal according to any one of
claims 1, 2 or 3, wherein said whole antibody or
single-chain Fv fragment or Fab fragment is a
polyclonal antibody, or fragment thereof, or a
monoclonal antibody, or fragment thereof.

25 [7] The crystal according to any one of
claims 1, 2 or 3, wherein said crystal is a carrier-
free pharmaceutical controlled release crystal.

[8] The crystal according to any one of claims 1, 2 or 3, wherein said antibody is selected from the group consisting of: chimeric antibodies, humanized antibodies, non-glycosylated antibodies, 5 bispecific antibodies, human antibodies and mouse antibodies.

[9] The crystal according to any one of claims 1, 2 or 3, wherein said antibody is selected from the group consisting of: IgG, IgM, IgA, IgD, IgE, 10 and serum IgA antibodies.

[10] The crystal according to claim 9, wherein said antibody is selected from the group consisting of: IgG1, IgG2, IgG3 and IgG4, IgM1 and IgM2, and IgA1 and IgA2 antibodies.

15 [11] The crystal according to any one of claims 1, 2 or 3, wherein said whole antibody or single-chain Fv antibody fragment or Fab antibody fragment has a greater half life in vivo than the soluble counterpart of said antibody or antibody 20 fragment.

[12] The crystal according to any one of claims 1, 2 or 3, wherein said antibody is an anti-idiotypic antibody.

25 [13] The crystal according to any one of claims 1, 2 or 3, wherein the antibody is selected from the group consisting of: Rituximab, Infliximab and Trastuzumab.

[14] The crystal according to any one of

claims 1, 2 or 3, wherein the antibody is selected from the group consisting of:

- Abciximab,
- Palivizumab,
- 5 Murumonab-CD3,
- Gemptuzumab,
- Trastuzumab,
- Basiliximab,
- Daclizumab,
- 10 Etanercept, and
- Ibritumomab tiuxetan.

[15] The crystal according to any one of claims 1, 2 or 3, wherein said antibody is selected from the group consisting of: anti-TNF antibodies,

- 15 anti-CD3 antibodies, anti-CD20 antibodies, anti-CD25 antibodies, anti-CD33 antibodies, anti-CD40 antibodies anti-HER2 antibodies, anti-HBV antibodies, anti-HAV antibodies, anti-HCV antibodies, anti-GPIIb/IIIa receptor antibodies, anti-RSV antibodies, anti-HIV antibodies,
- 20 anti-HSV antibodies and anti-EBV antibodies.

[16] The crystal according to any one of claims 1, 2 or 3, wherein said antibody is selected from the group consisting of: antibodies for treating

- 25 cardiovascular disease, antibodies for treating respiratory disease, antibodies for treating tissue transplant rejection, antibodies for treating organ transplant rejection, antibodies for treating cancer, antibodies for treating inflammatory disease and
- 30 antibodies used in radioimmunotherapy.

[17] The crystal according to any one of

claims 1, 2 or 3, wherein said crystal is labelled.

[18] The crystal according to claim 17,
wherein said crystal is labelled with a label selected
from the group consisting of radiolabels, enzyme
5 labels, toxins, magnetic agents or drug conjugates.

[19] A dried crystal of a whole antibody.

[20] A dried crystal of a single-chain Fv
fragment of an antibody or an Fab fragment of an
antibody.

10 [21] A composition for the release of a
whole antibody, a single-chain Fv antibody fragment, or
an Fab antibody fragment, said composition comprising:
15 (a) a whole antibody crystal, a single-chain
Fv antibody fragment crystal, or an Fab antibody
fragment crystal, and
(b) at least one polymeric carrier.

[22] A formulation, said formulation
comprising:

20 (a) a whole antibody crystal, a single-chain
Fv antibody fragment crystal, or an Fab antibody
fragment crystal, and
(b) at least one ingredient.

25 [23] A composition for the release of a
whole antibody, a single-chain Fv antibody fragment, or
an Fab antibody fragment, said composition comprising:
(a) a formulation, wherein said formulation
comprises a whole antibody crystal, a single-chain Fv

antibody fragment crystal, or an Fab antibody fragment crystal, and an ingredient; and

(b) at least one polymeric carrier.

5 [24] The crystal according to any one
of claims 1, 2 or 3, or the composition according to
claim 21 or 23, or the formulation according to claim
22, wherein said crystal or composition or formulation
has an antibody or antibody fragment crystal
10 concentration greater than about 1 mg/ml.

[25] The crystal according to any one
of claims 1, 2 or 3, or the composition according to
claim 21 or 23, or the formulation according to claim
22, wherein said crystal or composition or formulation
15 has an antibody or antibody fragment crystal
concentration greater than about 10.1 mg/ml.

[26] The crystal according to any one
of claims 1, 2 or 3, or the composition according to
claim 21 or 23, or the formulation according to claim
20 22, wherein said crystal or composition or formulation
has an antibody or antibody fragment crystal
concentration greater than about 20 mg/ml.

[27] The crystal according to any one
of claims 1, 2 or 3, or the composition according to
25 claim 21 or 23, or the formulation according to claim
22, wherein said crystal or composition or formulation
has an antibody or antibody fragment crystal
concentration greater than about 50 mg/ml.

[28] The crystal according to any one

of claims 1, 2 or 3, or the composition according to
claim 21 or 23, or the formulation according to claim
22, wherein said crystal or composition or formulation
has an antibody or antibody fragment crystal
5 concentration greater than about 100 mg/ml.

[29] The crystal according to any one
of claims 1, 2 or 3, or the composition according to
claim 21 or 23, or the formulation according to claim
22, wherein said crystal or composition or formulation
10 has an antibody or antibody fragment crystal
concentration greater than about 120 mg/ml.

[30] The crystal according to any one
of claims 1, 2 or 3, or the composition according to
claim 21 or 23, or the formulation according to claim
15 22, wherein said crystal or composition or formulation
has an antibody or antibody fragment crystal
concentration greater than about 200 mg/ml.

[31] The composition according to claim 21
or 23 or the formulation according to claim 22, wherein
20 said antibody or antibody fragment is a therapeutic
antibody or antibody fragment.

[32] The composition according to claim 21
or 23, wherein said polymeric carrier is a
biodegradable polymer.

25 [33] The composition according to claim 21
or 23, wherein said polymeric carrier is a
biocompatible polymer.

ingredient is selected from the group consisting of sucrose, trehalose, lactitol, gelatin, hydroxypropyl- β -cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

5 [40] A method for treating a mammal comprising the step of administering to the mammal an effective amount of a whole antibody crystal, a single-chain Fv antibody fragment crystal, or an Fab antibody fragment crystal.

10 [41] A method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition according to claim 21 or 23, or the formulation according to claim 22.

15 [42] The method according to claim 41, wherein the composition or formulation is administered by parenteral route, oral route, or by needle-free injection.

20 [43] A large-batch crystallization method for crystallizing a whole antibody, a single-chain Fv antibody fragment or an Fab antibody fragment, comprising the steps of:

25 (a) mixing a solution of a whole antibody, a single-chain Fv antibody fragment or an Fab antibody fragment with a crystallization solution or a crystallization buffer; and

(b) agitating said mixture for between about 3 and about 48 hours at a temperature between about -21°C and about 61°C, until crystals of said antibody or said antibody fragment are formed.

[34] The composition according to claim 21 or 23, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of:
5 poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (β-hydroxybutyrate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl)methacrylamide, poly 10 [(organo)phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride-alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid,
15 oligosaccharides, glycaminoglycans, sulfated polysaccharides, blends and copolymers thereof.

[35] The composition according to claim 21 or 23, wherein said polymeric carrier is poly(lactic-co-glycolic acid).

20 [36] The composition according to claim 21 or 23, wherein said polymeric carrier is emulsified with poly(vinyl alcohol).

[37] The composition according to claim 21 or 23, wherein said polymeric carrier is a co-polymer.

25 [38] The formulation according to claim 22 or the composition according to claim 23, wherein said ingredient is albumin.

[39] The formulation according to claim 22 or the composition according to claim 23, wherein said

[44] The large-batch crystallization method according to claim 43, further comprising the step of drying said crystals by a method selected from the group consisting of: air drying, spray drying, 5 lyophilization, vacuum oven drying and nitrogen gas drying.

[45] The large-batch crystallization method according to claim 43, wherein said temperature is between about 4°C and about 37°C.

10 [46] The large-batch crystallization method according to claim 43, wherein said temperature is between about -20°C to about 4°C.

15 [47] The large-batch crystallization method according to claim 43, wherein said temperature is between about 22°C and about 61°C.

[48] The large-batch crystallization method according to claim 43, wherein the pH of said crystallization buffer is within a range from about pH 1.9 to about pH 11.1.

20 [49] The large-batch crystallization method according to claim 43, wherein the pH of said crystallization buffer is within a range from about pH 1.9 to about pH 4.0.

25 [50] The large-batch crystallization method according to claim 43, wherein the pH of said crystallization buffer is between about pH 3 and about pH 10.

[51] The large-batch crystallization method according to claim 43, wherein the pH of said crystallization buffer is within a range from about pH 9.0 to about pH 11.1.

5 [52] The large-batch crystallization method according to claim 43, wherein the polyethylene glycol (PEG) concentration (w/v) between about 5 and about 40%.

10 [53] The large-batch crystallization method according to claim 43, wherein said crystallization buffer contains a polyethylene glycol (PEG) concentration (w/v) between about 1.9% and about 80%.

15 [54] The large-batch crystallization method according to claim 43, wherein said crystallization buffer contains a polyethylene glycol (PEG) concentration (w/v) between about 1.9% and about 5%.

20 [55] The large-batch crystallization method according to claim 43, wherein said crystallization buffer contains a polyethylene glycol (PEG) concentration (w/v) between about 20% and about 81%.

25 [56] The large-batch crystallization method according to claim 43, wherein said crystallization buffer comprises polyethylene glycol (PEG) of a size ranging between about 200 and about 20000.

[57] The large-batch crystallization method according to claim 43, wherein said crystallization buffer comprises polyethylene glycol (PEG) of a size between about 200 and about 80,000.

5 [58] The large-batch crystallization method according to claim 43, wherein said crystallization buffer comprises polyethylene glycol (PEG) of a size between about 200 to about 400.

10 [59] The large-batch crystallization method according to claim 43, wherein said crystallization buffer comprises polyethylene glycol (PEG) of a size between about 400 to about 80,000.

15 [60] The large-batch crystallization method according to claim 43, wherein the concentration in said solution of the antibody or single-chain Fv antibody fragment or Fab antibody fragment to be crystallized is between about 0.01 mg/ml and about 500 mg/ml.

20 [61] The large-batch crystallization method according to claim 43, wherein the concentration of the antibody or single-chain Fv antibody fragment or Fab antibody fragment to be crystallized is between about 0.01 mg/ml and about 4 mg/ml.

25 [62] The large-batch crystallization method according to claim 43, wherein the concentration of the antibody or single-chain Fv antibody fragment or Fab antibody fragment to be crystallized is between above about 10 mg/ml and about 25 mg/ml.

[63] The large-batch crystallization method according to claim 43, wherein the concentration of the antibody or single-chain Fv antibody fragment or Fab antibody fragment to be crystallized is between
5 about 3 mg/ml and about 200 mg/ml.

[64] The large-batch crystallization method according to claim 43, wherein the concentration of the antibody or single-chain Fv antibody fragment or Fab antibody fragment to be crystallized is between
10 above about 25 mg/ml and about 500 mg/ml.

[65] The large-batch crystallization method according to claim 43, wherein said crystallization buffer has a salt content between about 10 mM and about 400 mM.

15 [66] The large-batch crystallization method according to claim 43, wherein said crystallization buffer has a buffer concentration between about 0 mM and about 4 M.

20 [67] The large-batch crystallization method according to claim 43, wherein said crystallization buffer has a buffer concentration between about 0 mM and about 2 mM.

25 [68] The large-batch crystallization method according to claim 43, wherein said crystallization buffer has a buffer concentration between about 1 M and about 4 M.

[69] A method for purifying a protein by

affinity matrix purification, said method comprising the steps of:

- (a) mixing with a binding buffer crystals of a whole antibody, a single-chain Fv antibody fragment or an Fab antibody fragment, wherein said antibody or antibody fragment has affinity for the protein to be purified;
- (b) adding a protein solution comprising the protein to be purified to the crystal/buffer mixture;
- 10 (c) incubating the protein/crystal/buffer mixture for a time and at a temperature sufficient to permit binding of the protein to the antibody or antibody fragment;
- (d) washing the mixture with a wash buffer;
- 15 and
- (e) eluting the protein from the mixture with an elution buffer.

[70] A diagnostic kit for the *in vitro* detection of an antigen in a sample, said kit comprising:

- (a) a crystal of a whole antibody, a crystal of a single-chain Fv antibody fragment or a crystal of an Fab antibody fragment, wherein said antibody fragment is capable of specifically binding to 25 said antigen; and
- (b) one or more reagents for detecting the binding of said antibody crystal or antibody fragment crystal to any antigen in said sample.

[71] The diagnostic kit according to claim 30 70, wherein said antigen is a viral antigen.

[72] An *in vitro* diagnostic method for

detecting the presence of an antigen in a sample comprising the steps of:

- (a) contacting said sample with a crystal of a whole antibody, a crystal of a single-chain Fv antibody fragment or a crystal of an Fab antibody fragment, wherein said antibody or antibody fragment is capable of specifically binding to said antigen, under conditions which permit said antibody crystal or antibody fragment crystal to bind to any antigen in said sample; and

(b) detecting the binding of said antibody crystal or antibody fragment to any antigen in said sample.

- [73] The diagnostic method according to claim 72, wherein said antigen is a viral antigen.

[74] A large-batch crystallization method for crystallizing a whole antibody, a single-chain Fv antibody fragment or an Fab antibody fragment, comprising the steps of:

- (a) mixing a solution of a whole antibody, a single-chain Fv antibody fragment or an Fab antibody fragment with a crystallization solution or crystallization buffer; and

(b) agitating said mixture for between about 5 minutes and about 72 hours at a temperature between about -21°C and about 61°C, until crystals of said antibody or said antibody fragment are formed.

- [75] The large-batch crystallization method according to claim 43, wherein said solution of antibody to be crystallized is produced by a method comprising the steps of:

- (a) centrifuging transgenic milk comprising a whole antibody to remove milk fat and produce skim transgenic milk; and
- (b) diluting the skim transgenic milk
- 5 obtained in step (a) with about 250 mM EDTA to produce a solution of clarified skim transgenic milk comprising said antibody.

[76] The composition according to claim 21 or 23, or the formulation according to claim 22,
10 wherein said whole antibody crystal, single-chain Fv antibody fragment crystal, or Fab antibody fragment crystal is crosslinked.

[77] A method for treating a mammal comprising the step of administering to the mammal an
15 effective amount of the composition according to claim 76.

[78] The method according to claim 77, wherein the composition is administered by parenteral route, oral route, or by needle-free injection.